# MICARDIS HCT- telmisartan and hydrochlorothiazide tablet
# Boehringer Ingelheim Pharmaceuticals, Inc.

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use MICARDIS HCT safely and effectively. See full prescribing information for MICARDIS HCT.**

**MICARDIS® HCT (telmisartan and hydrochlorothiazide tablets), for oral use**
**Initial U.S. Approval: 2000**

**WARNING: FETAL TOXICITY**

***See full prescribing information for complete boxed warning.***

- **When pregnancy is detected, discontinue MICARDIS HCT as soon as possible. (5.1, 8.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1)**

## INDICATIONS AND USAGE

- MICARDIS HCT is a combination of an angiotensin II receptor blocker (ARB) and a thiazide diuretic indicated for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)
- MICARDIS HCT is not indicated for initial therapy (1)

## DOSAGE AND ADMINISTRATION

- Usual starting dose is 80 mg/12.5 mg once daily (2.1)
- Titrate up to 160 mg/25 mg as needed (2.1)
- Initiate patients with biliary obstructive disorders or hepatic insufficiency at 40 mg/12.5 mg (2.2)

## DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg/12.5 mg, 80 mg/12.5 mg, 80 mg/25 mg (3)

## CONTRAINDICATIONS

- Hypersensitivity to telmisartan or any component (4)
- Anuria (4)
- Co-Administration with aliskiren in patients with diabetes (4)

## WARNINGS AND PRECAUTIONS

- Avoid fetal or neonatal exposure (5.1)
- Correct volume or salt depletion before initiating therapy. Observe for signs and symptoms of hypotension (5.2)
- Monitor renal function and potassium in susceptible patients (5.3)
- Observe for clinical signs of fluid or electrolyte imbalance (5.4)
- Hypersensitivity Reaction (5.5)
- Acute Myopia and Secondary Angle-Closure Glaucoma (5.6)

## ADVERSE REACTIONS

The most common adverse reactions (≥2% of patients) were upper respiratory tract infection, dizziness, sinusitis, diarrhea, fatigue, influenza-like symptoms, and nausea (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

## DRUG INTERACTIONS

- Lithium: Risk of lithium toxicity (7.2)
- Non-steroidal anti-inflammatory drugs (NSAIDs): Reduced diuretic, natriuretic, and antihypertensive effects; increased risk of renal impairment (7.3)
- Dual blockade of renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7.4)
- Antidiabetic drugs: Dosage adjustment may be required (7.6)
- Cholestyramine and colestipol: Reduced absorption of thiazides (7.7)

## USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed during treatment with MICARDIS HCT (8.2)
- Severe Hepatic Impairment: Use not recommended (8.6)
- Severe Renal Impairment: Use not recommended (8.7)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 8/2020**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

**WARNING: FETAL TOXICITY**

- **When pregnancy is detected, discontinue MICARDIS HCT as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.**

## 1 INDICATIONS AND USAGE

MICARDIS HCT (telmisartan and hydrochlorothiazide) is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the classes to which this drug principally belongs. There are no controlled trials demonstrating risk reduction with MICARDIS HCT.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy *[see Clinical Studies (14)]*.

MICARDIS HCT is not indicated for initial therapy for the treatment of hypertension *[see Dosage and*

*Administration (2.1)].*

MICARDIS HCT may be used alone or in combination with other antihypertensive agents.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

Initiate a patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg on MICARDIS HCT, 80 mg/12.5 mg once daily. Dose can be titrated up to 160 mg/25 mg after 2 to 4 weeks, if necessary.

Initiate a patient whose blood pressure is not adequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen on MICARDIS HCT 80 mg/12.5 mg once daily. Dose can be titrated up to 160 mg/25 mg after 2 to 4 weeks, if necessary.

Patients titrated to the individual components (telmisartan and hydrochlorothiazide) may instead receive the corresponding dose of MICARDIS HCT.

MICARDIS HCT may be administered with other antihypertensive drugs.

### 2.2 Dose Adjustment for Hepatic Impairment

Initiate patients with biliary obstructive disorders or hepatic insufficiency under close medical supervision using the 40 mg/12.5 mg combination. MICARDIS HCT tablets are not recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

### 2.3 Important Administration Instructions

MICARDIS HCT tablets should not be removed from blisters until immediately before administration.

## 3 DOSAGE FORMS AND STRENGTHS

- 40 mg/12.5 mg, red and white tablets marked with the Boehringer Ingelheim logo and H4
- 80 mg/12.5 mg, red and white tablets marked with the Boehringer Ingelheim logo and H8
- 80 mg/25 mg, yellow and white tablets marked with the Boehringer Ingelheim logo and H9

## 4 CONTRAINDICATIONS

MICARDIS HCT is contraindicated:

- In patients who are hypersensitive to any component of this product *[see Warnings and Precautions (5.5)].*
- In patients with anuria.
- For co-administration with aliskiren in patients with diabetes *[see Drug Interactions (7.4)].*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Fetal Toxicity

*Telmisartan*

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When

pregnancy is detected, discontinue MICARDIS HCT as soon as possible.

*Hydrochlorothiazide*

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia *[see Use in Specific Populations (8.1)]*.

### 5.2 Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initialization of treatment with MICARDIS HCT. Correct volume or salt depletion prior to administration of MICARDIS HCT.

### 5.3 Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on MICARDIS HCT. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on MICARDIS HCT.

### 5.4 Electrolytes and Metabolic Disorders

Drugs, including telmisartan, that inhibit the renin-angiotensin system can cause hyperkalemia, particularly in patients with renal insufficiency, diabetes, or combination use with other angiotensin receptor blockers or ACE inhibitors and the concomitant use of other drugs that raise serum potassium levels *[see Drug Interactions (7.1, 7.4)]*.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

In controlled trials using the telmisartan/hydrochlorothiazide combination treatment, no patient administered 40 mg/12.5 mg, 80 mg/12.5 mg, or 80 mg/25 mg experienced a decrease in potassium ≥1.4 mEq/L, and no patient experienced hyperkalemia.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because telmisartan decreases uric acid, telmisartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

### 5.5 Hypersensitivity Reaction

*Hydrochlorothiazide*

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history *[see Contraindications (4)]*.

### 5.6 Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or

ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

### 5.7 Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

### 5.8 Postsympathectomy Patients

The antihypertensive effects of hydrochlorothiazide may be enhanced in the postsympathectomy patient.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling:

- Hypotension *[see Warnings and Precautions (5.2)]*
- Renal Impairment *[see Warnings and Precautions (5.3)]*
- Electrolytes and Metabolic Disorders *[see Warnings and Precautions (5.4)]*

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

MICARDIS HCT has been evaluated for safety in more than 1700 patients, including 716 treated for hypertension for longer than 6 months and 420 for more than 1 year. Adverse reactions have been limited to those that have been previously reported with telmisartan and/or hydrochlorothiazide.

Adverse reactions occurring at an incidence of ≥2% in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, are presented in Table 1 *[see Clinical Studies (14)]*.

**Table 1 Adverse Reactions Occurring at an Incidence of ≥2% in Patients Treated with Telmisartan/Hydrochlorothiazide and at a Greater Rate Than in Patients Treated with Placebo***

| | Telmisartan/Hydrochlorothiazide (n = 414) | Placebo (n = 74) | Telmisartan (n = 209) | Hydrochlorothiazide (n = 121) |
|---|---|---|---|---|
| **Body as a whole** | | | | |
| Fatigue | 3% | 1% | 3% | 3% |
| Influenza-like symptoms | 2% | 1% | 2% | 3% |
| **Central/Peripheral nervous system** | | | | |
| Dizziness | 5% | 1% | 4% | 6% |
| **Gastrointestinal system** | | | | |
| Diarrhea | 3% | 0% | 5% | 2% |
| Nausea | 2% | 0% | 1% | 2% |
| **Respiratory system disorder** | 4% | 3% | 3% | 6% |

| | | | | |
|---|---|---|---|---|
| Sinusitis | | | | |
| Upper respiratory tract infection | 8% | 7% | 7% | 10% |

* includes all doses of telmisartan (20 to 160 mg), hydrochlorothiazide (6.25 to 25 mg), and combinations thereof

Other adverse reactions observed for telmisartan/hydrochlorothiazide were: pain (including back and abdominal), dyspepsia, erythema, vomiting, bronchitis, and pharyngitis.

Adverse reactions occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

*Telmisartan*

Other adverse events that have been reported with telmisartan are listed below:

*Autonomic Nervous System:* impotence, increased sweating, flushing

*Body as a Whole:* allergy, fever, leg pain, chest pain

*Cardiovascular:* palpitation, angina pectoris, abnormal ECG, hypertension, peripheral edema

*Central Nervous System:* insomnia, somnolence, migraine, paresthesia, involuntary muscle contractions, hypoesthesia

*Gastrointestinal:* flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroesophageal reflux, toothache

*Hepato-biliary:* elevations of liver enzymes or serum bilirubin

*Metabolic:* gout, hypercholesterolemia, diabetes mellitus

*Musculoskeletal:* arthritis, arthralgia, leg cramps, myalgia

*Psychiatric:* anxiety, depression, nervousness

*Resistance Mechanism:* infection, abscess, otitis media

*Respiratory:* asthma, rhinitis, dyspnea, epistaxis

*Skin:* dermatitis, eczema, pruritus

*Urinary:* micturition frequency, cystitis

*Vascular:* cerebrovascular disorder

*Special Senses:* abnormal vision, conjunctivitis, tinnitus, earache

*Hydrochlorothiazide*

Other adverse events that have been reported with hydrochlorothiazide are listed below:

*Body as a Whole:* weakness

*Digestive:* pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

*Hematologic:* aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

*Hypersensitivity:* purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

*Metabolic:* hyperglycemia, glycosuria

*Musculoskeletal:* muscle spasm

*Nervous System/Psychiatric:* restlessness

*Renal:* interstitial nephritis

*Skin:* erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

*Special Senses:* transient blurred vision, xanthopsia

*Clinical Laboratory Findings*

Creatinine, Blood Urea Nitrogen (BUN): Increases in BUN (≥11.2 mg/dL) and serum creatinine (≥0.5 mg/dL) were observed in 2.8% and 1.4%, respectively, of patients with essential hypertension treated with MICARDIS HCT tablets in controlled trials. No patient discontinued treatment with MICARDIS HCT tablets because of an increase in BUN or creatinine *[see Warnings and Precautions (5.3)]*.

**6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of MICARDIS HCT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

*Blood and Lymphatic System Disorders:* eosinophilia

*Cardiac Disorders:* atrial fibrillation, congestive heart failure, myocardial infarction, tachycardia, bradycardia

*Ear and Labyrinth Disorders:* vertigo

*General Disorders and Administration Site Conditions:* asthenia, edema

*Hepato-biliary:* Abnormal hepatic function/liver disorder

*Immune System Disorders:* anaphylactic reaction

*Infections and Infestations:* urinary tract infection

*Investigations:* increased CPK

*Metabolism and Nutrition Disorders:* hypoglycemia (in diabetic patients)

*Musculoskeletal and Connective Tissue Disorders:* tendon pain (including tendonitis, tenosynovitis), rhabdomyolysis

*Nervous System Disorders:* syncope, headache

*Renal and Urinary Disorders:* renal failure, renal impairment including acute renal failure

*Reproductive System and Breast Disorders:* erectile dysfunction

*Respiratory, Thoracic and Mediastinal Disorders:* coughing

*Skin and Subcutaneous Tissue Disorders:* drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), angioedema (with fatal outcome)

*Vascular Disorder:* orthostatic hypotension

**Non-melanoma Skin Cancer**

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

## 7 DRUG INTERACTIONS

### 7.1 Agents Increasing Serum Potassium

Co-administration of telmisartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

### 7.2 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of thiazide diuretics or angiotensin II receptor antagonists, including telmisartan. Monitor lithium levels in patients receiving MICARDIS HCT and lithium.

### 7.3 Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors

*Telmisartan*

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs may be attenuated by NSAIDs. Therefore, monitor renal function and blood pressure periodically in patients receiving MICARDIS HCT and NSAIDs.

*Hydrochlorothiazide*

Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Therefore, when MICARDIS HCT and non-steroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

### 7.4 Dual Blockade of the Renin-Angiotensin-Aldosterone System and Changes in Renal Function

Dual blockade of the renin-angiotensin-aldosterone system (RAS) with angiotensin blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and renal impairment. The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan (ARB) only, ramipril (ACE inhibitor) only, or the combination, and followed them for a median of 56 months. Patients who received the combination of ARB and ACE inhibitor did not obtain any additional benefit (no additional reduction of risk of cardiovascular death, myocardial infarction, stroke, or hospitalization from heart failure) compared to ARB monotherapy or ACE inhibitor monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with monotherapy groups.

In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on MICARDIS HCT and other agents that affect the RAS.

Do not co-administer aliskiren with MICARDIS HCT in patients with diabetes. Avoid concomitant use of aliskiren with MICARDIS HCT in patients with renal impairment (GFR <60 mL/min/1.73 $m^2$).

### 7.5 Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitor digoxin levels in patients taking concomitant MICARDIS HCT and digoxin.

### 7.6 Antidiabetic Drugs (Oral Agents and Insulin)

Dosage adjustment of antidiabetic drugs may be required when co-administered with hydrochlorothiazide.

### 7.7 Cholestyramine and Colestipol Resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

MICARDIS HCT can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death *(see Clinical Considerations)*. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Studies in rats and rabbits with telmisartan showed fetotoxicity only at maternally toxic doses *(see Data)*. When pregnancy is detected, discontinue MICARDIS HCT as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

*Disease-associated maternal and/or embryo/fetal risk*

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

*Fetal/Neonatal adverse reactions*

*Telmisartan*

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking MICARDIS HCT during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue MICARDIS HCT, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to MICARDIS HCT for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function *[see Use in Specific Populations (8.4)]*.

*Hydrochlorothiazide*

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

Data

*Animal Data*

*MICARDIS HCT*

A developmental toxicity study was performed in rats with telmisartan/hydrochlorothiazide doses of 3.2/1.0, 15/4.7, 50/15.6, and 0/15.6 mg/kg/day. Although the two higher dose combinations appeared to be more toxic (significant decrease in body weight gain) to the dams than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

*Telmisartan*

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day. In rabbits, embryo lethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day (approximately 12 times the maximum recommended human dose [MRHD] of 80 mg on a $mg/m^2$ basis). In rats, maternally toxic (reduced body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (approximately 1.9 times the MRHD on a $mg/m^2$ basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no-observed-effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are approximately 0.64 and 3.7 times, respectively, on a $mg/m^2$ basis, the MRHD of telmisartan (80 mg/day).

*Hydrochlorothiazide*

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively (about 600 and 400 times the MRHD), provided no evidence of harm to the fetus.

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times that in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre-eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications (e.g., heart disease) in pregnancy should be avoided.

### 8.2 Lactation

Risk Summary

There is no information regarding the presence of MICARDIS HCT or telmisartan in human milk, the effects on the breastfed infant or the effects on milk production. Limited published studies report that hydrochlorothiazide is present in human milk. However, there is insufficient information to determine the effects of hydrochlorothiazide on the breastfed infant or the effects of hydrochlorothiazide on milk production. Telmisartan is present in the milk of lactating rats *(see Data)*. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with MICARDIS HCT.

Data

Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration.

### 8.4 Pediatric Use

Safety and effectiveness of MICARDIS HCT in pediatric patients have not been established.

Neonates with a history of *in utero* exposure to MICARDIS HCT:

If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

### 8.5 Geriatric Use

In the controlled clinical trials (n=1017), approximately 20% of patients treated with telmisartan/hydrochlorothiazide were 65 years of age or older, and 5% were 75 years of age or older. No overall differences in effectiveness and safety of telmisartan/hydrochlorothiazide were observed in these patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

### 8.6 Use in Patients with Hepatic Impairment

Patients with biliary obstructive disorders or hepatic insufficiency should initiate treatment under close medical supervision using the 40 mg/12.5 mg combination.

*Telmisartan*

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance and higher blood levels.

*Hydrochlorothiazide*

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

### 8.7 Use in Patients with Renal Impairment

Safety and effectiveness of MICARDIS HCT in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. In patients with severe renal impairment, MICARDIS HCT tablets are not recommended. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

## 10 OVERDOSAGE

*Telmisartan*

Limited data are available with regard to overdosage of telmisartan in humans. The most likely manifestations of overdosage with telmisartan are hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

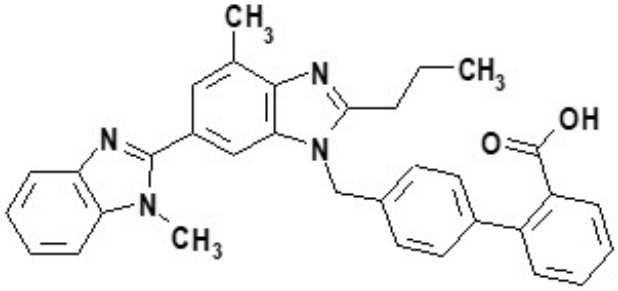
*Hydrochlorothiazide*

The most common signs and symptoms observed in patients with a hydrochlorothiazide overdose are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral $LD_{50}$ of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

## 11 DESCRIPTION

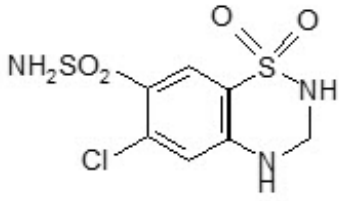
MICARDIS HCT tablets are a combination of telmisartan, an orally active angiotensin II antagonist acting on the $AT_1$ receptor subtype, and hydrochlorothiazide, a thiazide diuretic.

Telmisartan, a non-peptide molecule, is chemically described as 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder with a molecular weight of 297.74. It is slightly soluble in water, and freely soluble in sodium hydroxide solution. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



MICARDIS HCT tablets are formulated for oral administration in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg, and 80 mg/25 mg telmisartan and hydrochlorothiazide, respectively. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, maize starch, and sodium starch glycolate. As coloring agents, the 40 mg/12.5 mg and 80 mg/12.5 mg tablets contain ferric oxide red, and the 80 mg/25 mg tablets contain ferric oxide yellow. MICARDIS HCT tablets are hygroscopic and require protection from moisture.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

*MICARDIS HCT*

MICARDIS HCT is a combination of two drugs with antihypertensive properties: a thiazide diuretic, hydrochlorothiazide, and an angiotensin II receptor blocker (ARB), telmisartan.

*Telmisartan*

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the $AT_1$ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an $AT_2$ receptor found in many tissues, but $AT_2$ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000-fold) for the $AT_1$ receptor than for the $AT_2$ receptor.

Telmisartan does not inhibit ACE (kininase II) nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

*Hydrochlorothiazide*

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an ARB tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood.

**12.2 Pharmacodynamics**

*Telmisartan*

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by approximately 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium) or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

The antihypertensive effects of telmisartan have been studied in six placebo-controlled clinical trials including a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95 to 114 mmHg), 1031 of whom were treated with telmisartan. Following once-daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

The onset of antihypertensive activity occurs within 3 hours, with a maximal reduction by approximately 4 weeks. At doses of 20, 40, and 80 mg, the antihypertensive effect of once-daily administration of telmisartan was maintained for the full 24-hour dose interval.

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

*Hydrochlorothiazide*

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours, and lasts approximately 6 to 12 hours.

Drug Interactions

*Hydrochlorothiazide*

*Alcohol, barbiturates, or narcotics:* Potentiation of orthostatic hypotension may occur.

*Skeletal muscle relaxants:* Possible increased responsiveness to muscle relaxants such as curare derivatives.

*Corticosteroids, ACTH:* Intensified electrolyte depletion, particularly hypokalemia.

*Pressor amines (e.g., norepinephrine):* Possible decreased response to pressor amines but not sufficient to preclude their use.

**12.3 Pharmacokinetics**

*Telmisartan*

*Absorption:*

Following oral administration, peak concentrations ($C_{max}$) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of approximately 6% with 40 mg and approximately 20% after a 160 mg dose. MICARDIS HCT can be administered with or without food. The absolute bioavailability of telmisartan is dose dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of telmisartan with orally administered MICARDIS are nonlinear over the dose range 20 mg to 160 mg, with greater than proportional increases of plasma concentrations ($C_{max}$ and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once-daily dosing are approximately 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once-daily dosing.

*Distribution:*

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and $\alpha_1$-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding.

*Metabolism:*

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

*Elimination:*

Following either intravenous or oral administration of $^{14}C$-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

*Hydrochlorothiazide*

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Specific Populations

*Telmisartan*

*Renal Insufficiency:* Telmisartan is not removed from blood by hemofiltration *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.7)]*.

*Hepatic Insufficiency:* In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% *[see Use in Specific Populations (8.6)]*.

*Gender:* Plasma concentrations of telmisartan are generally 2 to 3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

*Geriatric Patients:* The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years of age.

Drug Interaction Studies

*Telmisartan*

*Ramipril:* Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state $C_{max}$ and AUC of ramipril 2.3- and 2.1-fold, respectively, and $C_{max}$ and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, $C_{max}$ and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.

*Other Drugs:* Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Telmisartan and Hydrochlorothiazide*

No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of telmisartan and hydrochlorothiazide.

*Telmisartan*

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a $mg/m^2$ basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD of telmisartan (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a $mg/m^2$ basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

*Hydrochlorothiazide*

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology

Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, in the Mouse Lymphoma Cell (mutagenicity) assay, and in the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

## 14 CLINICAL STUDIES

*Telmisartan and Hydrochlorothiazide*

In controlled clinical trials with more than 2500 hypertensive patients, 1017 patients were exposed to telmisartan (20 mg to 160 mg) and concomitant hydrochlorothiazide (6.25 mg to 25 mg). These trials included one factorial trial (Study 1) with combinations of telmisartan (20 mg, 40 mg, 80 mg, 160 mg, or placebo) and hydrochlorothiazide (6.25 mg, 12.5 mg, 25 mg, and placebo). The factorial trial randomized 818 patients, including 493 (60%) males; 596 (73%) Non-Black and 222 (27%) Blacks; and 143 (18%) ≥65 years of age (median age was 53 years old). The mean supine blood pressure at baseline for the total population was 154/101 mmHg.

The combination of telmisartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressures at trough of 16-21/9-11 mmHg for doses between 40 mg/12.5 mg and 80 mg/25 mg, compared with 9-13/7-8 mmHg for telmisartan 40 mg to 80 mg monotherapy and 4/4 mmHg for hydrochlorothiazide 12.5 mg monotherapy. The antihypertensive effect was independent of age or gender. There was essentially no change in heart rate in patients treated with the combination of telmisartan and hydrochlorothiazide in the placebo-controlled trial.

Four other studies of hypertensive patients of at least six months' duration allowed add-on of hydrochlorothiazide for patients who either were not adequately controlled on the randomized telmisartan monotherapy dose or had not achieved adequate blood pressure response after completing the up-titration of telmisartan. In active-controlled studies, the addition of 12.5 mg hydrochlorothiazide to titrated doses of telmisartan in patients who did not achieve or maintain adequate response with telmisartan monotherapy further reduced systolic and diastolic blood pressures.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

MICARDIS HCT is available in three strengths as biconvex two-layered, oblong-shaped, uncoated tablets containing telmisartan and hydrochlorothiazide:

- **40 mg/12.5 mg tablet:** red and white (may contain red specks) marked with the Boehringer Ingelheim company symbol and H4; individually blister-sealed in cartons of 30 tablets as 3 × 10 cards (NDC 0597-0043-37)
- **80 mg/12.5 mg tablet:** red and white (may contain red specks) marked with the Boehringer Ingelheim company symbol and H8; individually blister-sealed in cartons of 30 tablets as 3 × 10 cards (NDC 0597-0044-37)
- **80 mg/25 mg tablet:** yellow and white (may contain yellow specks) marked with the Boehringer Ingelheim company symbol and H9; individually blister-sealed in cartons of 30 tablets as 3 × 10

cards (NDC 0597-0042-37)

*Storage*

**Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)** [see USP Controlled Room Temperature]. Tablets should not be removed from blisters until immediately before administration.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

*Pregnancy*

Advise female patients of childbearing age about the consequences of exposure to MICARDIS HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

*Lactation*

Advise nursing women not to breastfeed during treatment with MICARDIS HCT *[see Use in Specific Populations (8.2)]*.

*Symptomatic Hypotension and Syncope*

Advise patients that lightheadedness can occur, especially during the first days of therapy, and to report it to their healthcare provider. Inform patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. Advise patients to contact their healthcare provider if syncope occurs *[see Warnings and Precautions (5.2)]*.

*Potassium Supplements*

Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing healthcare provider *[see Warnings and Precautions (5.4) and Drug Interactions (7.1)]*.

*Acute Myopia and Secondary Angle-Closure Glaucoma*

Advise patients to discontinue MICARDIS HCT and seek immediate medical attention if they experience symptoms of Acute Myopia or Secondary Angle-Closure Glaucoma *[see Warnings and Precautions (5.6)]*.

*Non-melanoma Skin Cancer*

Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

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Ridgefield, CT 06877 USA

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IT5825EH262020

**Patient Information**
**MICARDIS® HCT (my-CAR-dis HCT)**
**(telmisartan and hydrochlorothiazide tablets)**

Read this Patient Information before you start taking MICARDIS HCT tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

**What is the most important information I should know about MICARDIS HCT tablets?**

MICARDIS HCT can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking MICARDIS HCT, tell your doctor right away.

**What is MICARDIS HCT?**

MICARDIS HCT is a prescription medicine used to treat high blood pressure (hypertension).
MICARDIS HCT contains:

- telmisartan, an angiotensin receptor blocker (ARB)
- hydrochlorothiazide, a water pill or diuretic

Your doctor may prescribe other medicines for you to take along with MICARDIS HCT to treat your high blood pressure.

It is not known if MICARDIS HCT is safe and effective in children.

**Do not take MICARDIS HCT tablets if you:**

- have low or no urine output
- are allergic (hypersensitive) to the active ingredients (telmisartan or hydrochlorothiazide) or any of the other ingredients listed at the end of this leaflet

**What should I tell my doctor before using MICARDIS HCT tablets?**

Before you take MICARDIS HCT tablets, tell your doctor if you:

- are pregnant or are planning to become pregnant. See **"What is the most important information I should know about MICARDIS HCT tablets?"**
- are breast-feeding or plan to breast-feed. MICARDIS HCT can pass into your breast milk and may harm your baby. You and your doctor should decide if you will take MICARDIS HCT or breast-feed. You should not do both. Talk with your doctor about the best way to feed your baby if you take MICARDIS HCT tablets.
- have been told that you have abnormal body salt (electrolytes) levels in your blood
- have liver problems
- have asthma or history of asthma
- have lupus
- have diabetes
- have kidney problems
- have any other medical conditions

**Tell your doctor about all the medicines you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Also, tell your doctor if you drink alcohol.

MICARDIS HCT may affect the way other medicines work, and other medicines may affect how

MICARDIS HCT works. Especially tell your doctor if you take:

- aliskiren
- digoxin (Lanoxin®)
- lithium (Lithobid®, lithium carbonate, lithium citrate)
- other medicines used to treat your high blood pressure or a heart problem
- water pills (diuretic)
- aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- potassium supplements or a salt substitute containing potassium
- medicine used to treat diabetes, including insulin
- narcotic pain medicines
- sleeping pills
- steroid medicine or Adrenocorticotrophic Hormone (ACTH)
- barbiturates
- certain cholesterol lowering medicines (resins that are used for cholesterol reduction, e.g., cholestyramine and colestipol resins)

Ask your doctor if you are not sure if you are taking one of the medicines listed above.

Know the medicines you take. Keep a list of them and show it to your doctor or pharmacist when you get a new medicine.

**How should I take MICARDIS HCT tablets?**

- Take MICARDIS HCT tablets exactly as your doctor tells you to take it.
- Your doctor will tell you how much MICARDIS HCT to take and when to take it.
- Do not change your dose unless your doctor tells you to.
- Take MICARDIS HCT once each day.
- Take MICARDIS HCT tablets with or without food.
- If you take too much MICARDIS HCT, call your doctor, or go to the nearest hospital emergency room right away.
- Read the **"How to open the blister"** at the end of this leaflet before you use MICARDIS HCT. Talk with your doctor if you do not understand the instructions.

**What are the possible side effects of MICARDIS HCT tablets?**

**MICARDIS HCT tablets may cause serious side effects,** including:

- **Injury or death to your unborn baby.** See **"What is the most important information I should know about MICARDIS HCT tablets?"**
- **Low blood pressure (hypotension)** is most likely to happen if you also:
  - take water pills (diuretics)
  - are on a low-salt diet
  - get dialysis treatments
  - have heart problems
  - get sick with vomiting or diarrhea
  - do not drink enough fluids
  - sweat a lot

  **If you feel faint or dizzy, lie down and call your doctor right away.**
- **Kidney problems,** which may get worse if you already have kidney disease. You may have changes in your kidney test results, and you may need a lower dose of MICARDIS HCT tablets. Call your doctor if you get:
  - swelling in your feet, ankles, or hands
  - unexplained weight gain

  **Call your doctor right away if you get any of the symptoms listed above.**
- **Liver problems,** which may get worse in people who already have liver problems and take

MICARDIS HCT.

- **Eye problems**. One of the medicines in MICARDIS HCT can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting MICARDIS HCT. Tell your doctor right away if you have:
  - decrease in vision
  - eye pain
- **Allergic reactions.** Tell your doctor right away if you get any of these symptoms:
  - swelling of the face, tongue, throat
  - difficulty breathing
- **Worsening of lupus.** Tell your doctor if your lupus gets worse or becomes active while taking MICARDIS HCT.
- **Change in body salts (electrolytes) level in your blood and fluid problems.** Your doctor may do tests to check your blood. Call your doctor right away if you have:

  - dry mouth
  - thirst
  - tiredness
  - sleepiness
  - restlessness
  - confusion
  - seizures
  - fast heartbeats
  - weakness
  - muscle pain or cramps
  - very low urine output
  - nausea or vomiting

- **Skin Cancer.** One of the medicines in MICARDIS HCT may increase your risk of getting non-melanoma skin cancer. Protect your skin from the sun and undergo regular skin cancer screening when taking MICARDIS HCT.

**The most common side effects of MICARDIS HCT tablets include:**

- upper respiratory tract infections, including sinus pain/congestion and sore throat
- dizziness
- feeling tired
- flu-like symptoms
- back pain
- diarrhea
- nausea

These are not all the possible side effects with MICARDIS HCT tablets. Tell your doctor if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store MICARDIS HCT tablets?**

- Store MICARDIS HCT tablets at room temperature 68°F to 77°F (20°C to 25°C).
- Do not remove MICARDIS HCT tablets from blisters until right before you take them.

**Keep MICARDIS HCT tablets and all medicines out of the reach of children.**

**General information about MICARDIS HCT tablets:**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MICARDIS HCT tablets for a condition for which it was not prescribed. Do not give MICARDIS HCT tablets to other people, even if they have the same condition you have. It may harm them.

This Patient Information leaflet summarizes the most important information about MICARDIS HCT tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or

doctor for information about MICARDIS HCT tablets that is written for health professionals.

For current prescribing information, scan the code below or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

**What are the ingredients in MICARDIS HCT tablets?**

Active Ingredients: telmisartan and hydrochlorothiazide

Inactive Ingredients: sodium hydroxide, meglumine, povidone, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, maize starch, and sodium starch glycolate

The 40 mg/12.5 mg and 80 mg/12.5 mg tablets also contain: ferric oxide red.

The 80 mg/25 mg tablets also contain: ferric oxide yellow.

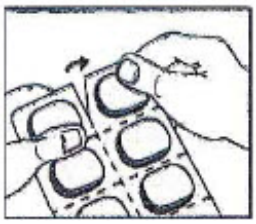
**What is high blood pressure (hypertension)?**

Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. Medicines that lower your blood pressure lower your chance of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood through the body and causes damage to the blood vessels. MICARDIS HCT tablets can help your blood vessels relax so your blood pressure is lower.

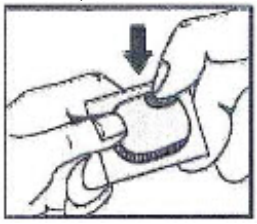
**How to open the blister:**

1. Tear (You may also use scissors to tear the blister apart)



2. Peel (Peel off the paper layer from the aluminum foil)

3. Push (Push the tablet through the aluminum foil)



This Patient Information has been approved by the U.S. Food and Drug Administration.

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Ingelheim, Germany



Revised: August 2020

IT5825EH262020

**PRINCIPAL DISPLAY PANEL - 40 mg/12.5 mg Tablet Blister Pack Carton**

NDC 0597-0043-37

Micardis® HCT
(telmisartan/
hydrochlorothiazide tablets)

40 mg/12.5 mg

Rx only

30 tablets - 3 blister cards of 10 tablets each.
Each tablet contains 40 mg of telmisartan and 12.5 mg of hydrochlorothiazide.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

Important: Moisture sensitive tablets - do not remove from blisters until immediately before administration.

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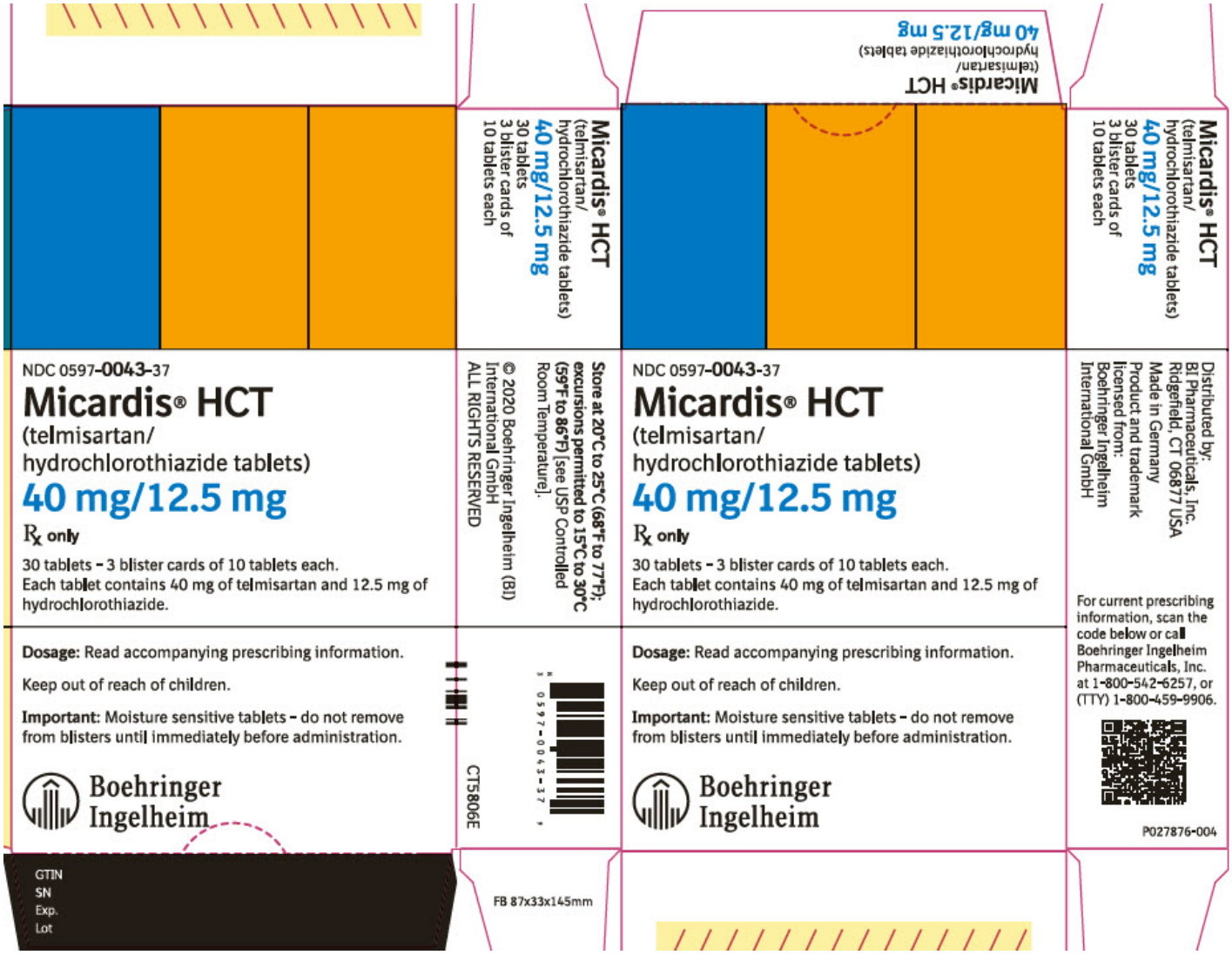


**PRINCIPAL DISPLAY PANEL - 80 mg/12.5 mg Tablet Blister Pack Carton**

NDC 0597-0044-37

Micardis® HCT
(telmisartan/
hydrochlorothiazide tablets)

80 mg/12.5 mg

Rx only

30 tablets - 3 blister cards of 10 tablets each.
Each tablet contains 80 mg of telmisartan and 12.5 mg of hydrochlorothiazide.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

Important: Moisture sensitive tablets - do not remove from blisters until immediately before administration.

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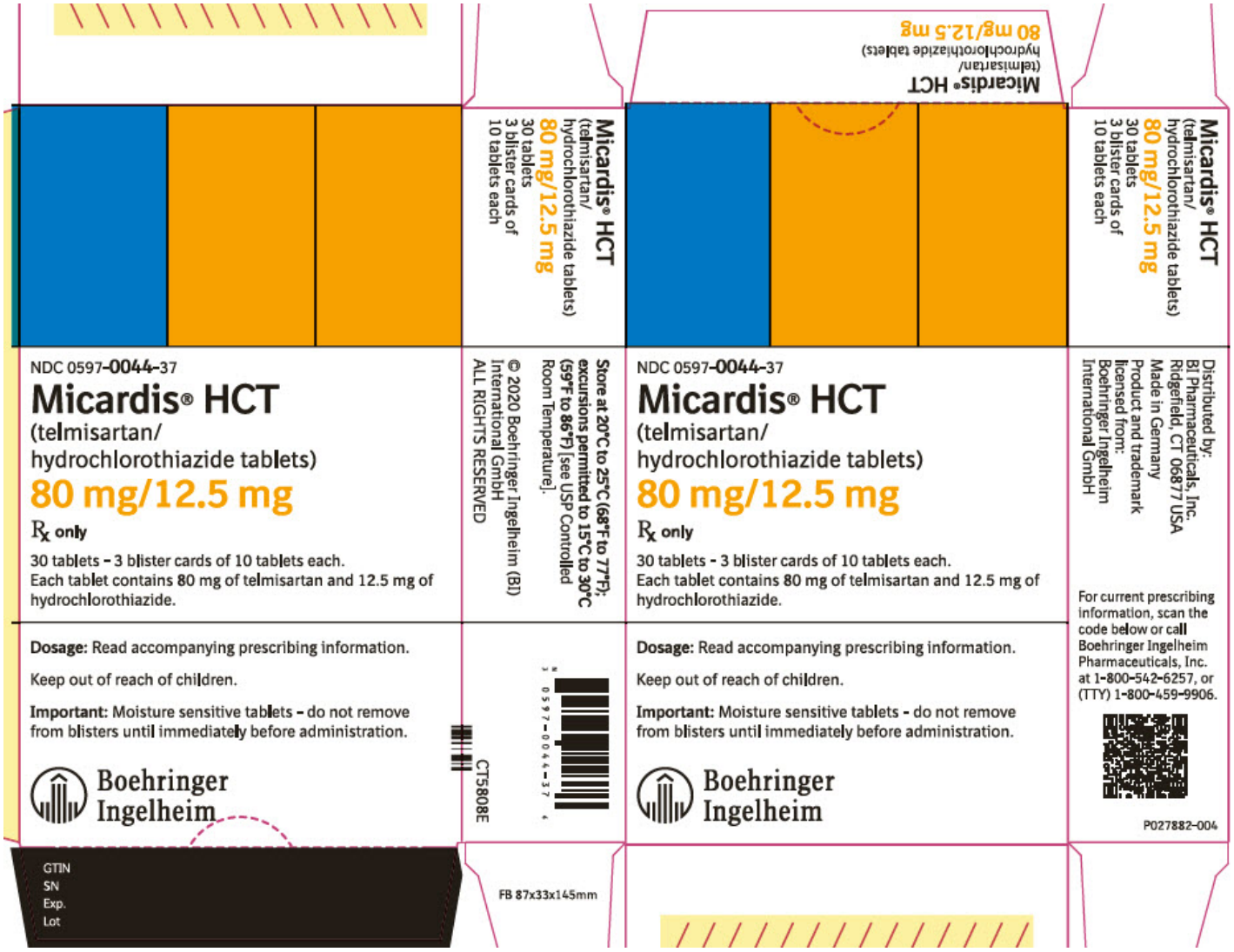
Ingelheim




**PRINCIPAL DISPLAY PANEL - 80 mg/25 mg Tablet Blister Pack Carton**

NDC 0597-0042-37

Micardis® HCT
(telmisartan/
hydrochlorothiazide tablets)

80 mg/25 mg

Rx only

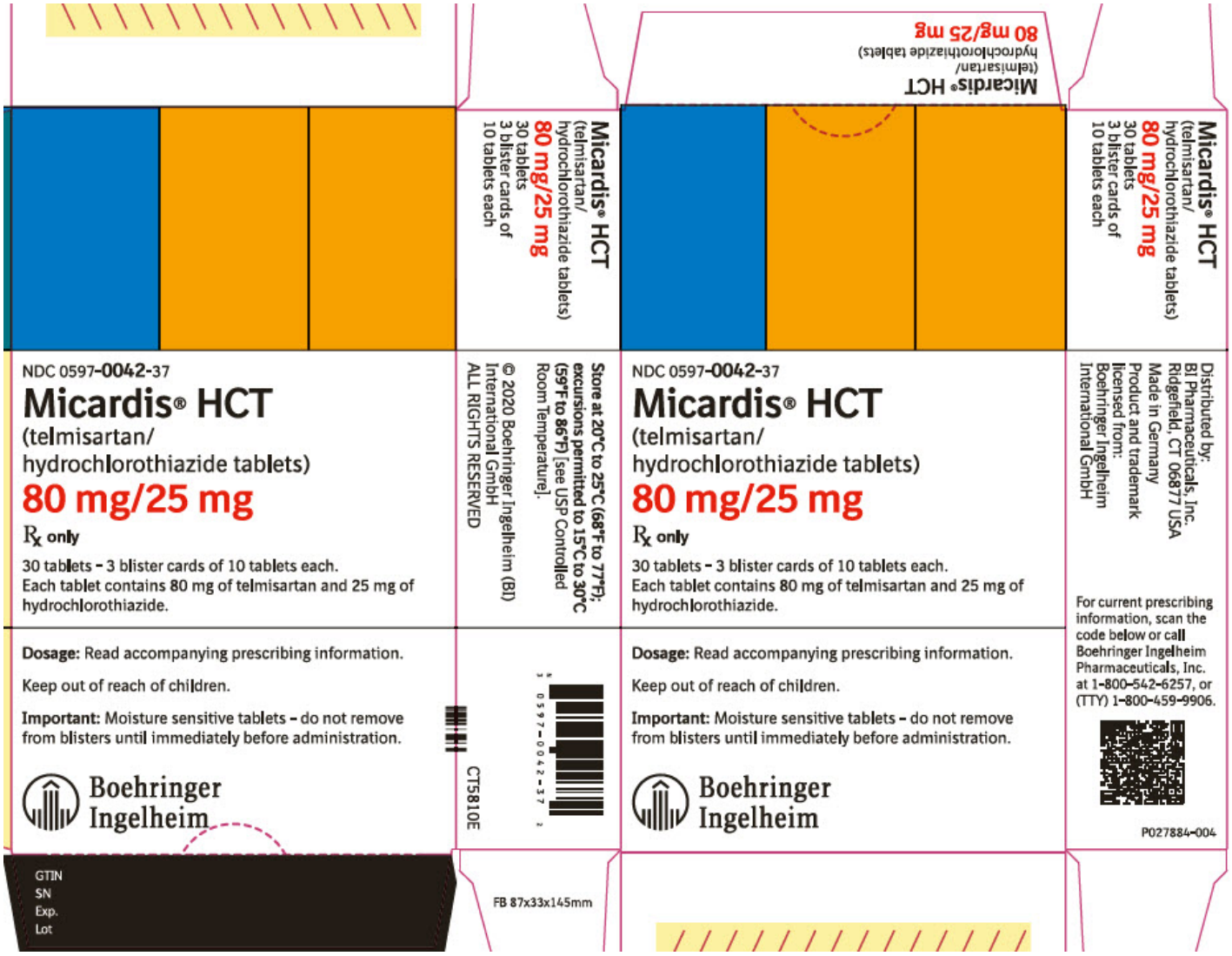
30 tablets - 3 blister cards of 10 tablets each.
Each tablet contains 80 mg of telmisartan and 25 mg of hydrochlorothiazide.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

Important: Moisture sensitive tablets - do not remove from blisters until immediately before administration.

Boehringer
Ingelheim




# MICARDIS HCT

telmisartan and hydrochlorothiazide tablet

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:0597-0043 |
| **Route of Administration** | ORAL | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **TELMISARTAN** (UNII: U5SYW473RQ) (TELMISARTAN - UNII:U5SYW473RQ) | TELMISARTAN | 40 mg |
| **HYDROCHLOROTHIAZIDE** (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH) | HYDROCHLOROTHIAZIDE | 12.5 mg |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | WHITE (WHITE) , RED (RED) | **Score** | no score |
| **Shape** | OVAL (OVAL) | **Size** | 14mm |
| **Flavor** | | **Imprint Code** | H4; |

| | |
|---|---|
| **Contains** | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:0597-0043-37 | 3 in 1 CARTON | 12/01/2000 | |
| **1** | | 10 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA021162 | 12/01/2000 | |

# MICARDIS HCT

telmisartan and hydrochlorothiazide tablet

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:0597-0044 |
| **Route of Administration** | ORAL | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **TELMISARTAN** (UNII: U5SYW473RQ) (TELMISARTAN - UNII:U5SYW473RQ) | TELMISARTAN | 80 mg |
| **HYDROCHLOROTHIAZIDE** (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH) | HYDROCHLOROTHIAZIDE | 12.5 mg |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | WHITE (WHITE) , RED (RED) | **Score** | no score |
| **Shape** | OVAL (OVAL) | **Size** | 16mm |
| **Flavor** | | **Imprint Code** | H8; |
| **Contains** | | | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:0597-0044-37 | 3 in 1 CARTON | 12/01/2000 | |
| **1** | | 10 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA021162 | 12/01/2000 | |

# MICARDIS HCT

telmisartan and hydrochlorothiazide tablet

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:0597-0042 |
| **Route of Administration** | ORAL | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **TELMISARTAN** (UNII: U5SYW473RQ) (TELMISARTAN - UNII:U5SYW473RQ) | TELMISARTAN | 80 mg |
| **HYDROCHLOROTHIAZIDE** (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH) | HYDROCHLOROTHIAZIDE | 25 mg |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | WHITE (WHITE) , YELLOW (YELLOW) | **Score** | no score |
| **Shape** | OVAL (OVAL) | **Size** | 16mm |
| **Flavor** | | **Imprint Code** | H9; |
| **Contains** | | | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:0597-0042-37 | 3 in 1 CARTON | 12/01/2000 | |
| **1** | | 10 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA021162 | 12/01/2000 | |

## Labeler - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

## Registrant - Boehringer Ingelheim Pharmaceuticals Inc. (603175944)

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Boehringer Ingelheim Pharma GmbH and Co. KG | | 551147440 | ANALYSIS(0597-0042, 0597-0043, 0597-0044) , API MANUFACTURE(0597-0042, 0597-0043, 0597-0044) , MANUFACTURE(0597-0042, 0597-0043, 0597-0044) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| West-Ward Columbus | | 058839929 | ANALYSIS(0597-0042, 0597-0043, 0597-0044) , LABEL(0597-0042, 0597-0043, 0597-0044) , MANUFACTURE(0597-0042, 0597-0043, 0597-0044) , PACK(0597-0042, 0597-0043, 0597- |

| | | | |
|---|---|---|---|
| Inc. | | | 0044) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Malgrat Pharma Chemicals, S.L.U. | | 468215759 | ANALYSIS(0597-0043, 0597-0044, 0597-0042) , API MANUFACTURE(0597-0043, 0597-0044, 0597-0042) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Rottendorf Pharma GmbH | | 315974691 | ANALYSIS(0597-0042, 0597-0043, 0597-0044) , LABEL(0597-0042, 0597-0043, 0597-0044) , MANUFACTURE(0597-0042, 0597-0043, 0597-0044) , PACK(0597-0042, 0597-0043, 0597-0044) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| ZAKLADY FARMACEUTYCZNE POLPHARMA S A | | 422195139 | API MANUFACTURE(0597-0042, 0597-0043, 0597-0044) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Boehringer Ingelheim Promeco S.A. de C.V. | | 812579472 | ANALYSIS(0597-0042, 0597-0043, 0597-0044) , LABEL(0597-0042, 0597-0043, 0597-0044) , PACK(0597-0042, 0597-0043, 0597-0044) |

Revised: 8/2020

Boehringer Ingelheim Pharmaceuticals, Inc.